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EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,780	KOLOSSOV ET AL.	
	Examiner	Art Unit	
	MARCIA S. NOBLE	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-80* is/are pending in the application.

4a) Of the above claim(s) *17-25,27-39,43,44,46-48,50-69 and 76-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,26,40-42,45,49 and 70-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 December 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/6/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-80 are pending. Claims 1, 4, 7-13, 15-19, 21-29, 31-34, 36, 37, 39, 40, 43-65, 68-74, 76-80 are amended and claim 81 is canceled by the amendment, filed 7/6/2009.

Election/Restrictions

Applicant's election with traverse of Group II in the reply filed on 7/6/2009 is acknowledged. The traversal is on the ground(s) that Rambhatla does not disclose the special technical feature of the invention because, contrary to Examiners interpretation, the EB formation disclosed by Rambhatla does not encompass "allowing the cells to integrate and align into a tissue like structure. Applicant further states that EB are not tissue-like structures but are an early step in the method which ultimately results in integration and alignment of at least two cell types into tissue or tissue-like structure as seen in figures 2B and 3C of the specification. Applicant further indicates that there is no search burden in examining all the groups together because the international search report provided and the only different between groups I and II are the cell type. This is not found persuasive because Applicant is not giving claim 1 its broadest reasonable interpretation. The specification does not define "integration", "alignment", "tissue" or "tissue-like structure". Given it broadest reasonable interpretation, the recitation, "allowing integration and alignment of said at least two cell types into a tissue or tissue-like structures", encompasses any situation wherein two or more cell types align or form

some type of structure. An EB is an aggregation of ES cell that grow into different cell types. Thus, the EB is an alignment and/or integration of more than one cell type into a structure. Further it can be considered tissue-like structure because a tissue is an organized or aligned group of multiple cell types. Thus contrary to Applicant assertion, an EB as disclosed by Rambhatla encompasses the limitations of the claim 1 and thus discloses the special technical feature of the invention. Further, the claims encompass multiple products and multiple methods, which is not an inventive category of inventions accepted as having unity of invention. Thus, the invention lacks unity for this reason as well. Applicant's argument of search burden is not found persuasive because in lack of unity search burden in not the means by which unity of invention or lack thereof is determined. Further, search additional inventions would comprise search multiple cell types, as well as potentially 100s of different regulatory elements, and culture conditions to each cell type. Thus, contrary to Applicant's assertion, search the additional groups would be considered a search burden.

Applicant elected Group II drawn to an in vitro cardiac tissue formation method. Thus, as previously stated in the restriction requirement, Group I and II are rejoined but considered within the scope of the elected for Group II.

The requirement is still deemed proper and is therefore made FINAL.

Claims 17-25, 27-39, 43, 44, 46-48, 50-69, and 76-80 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/6/2009.

Claims 1-16, 26, 40-42, 45, 49, and 70-75 are under consideration.

Specification

The disclosure is objected to because of the following informalities: The specification comprises typographical errors on p. 16, line 25, which recites "that the those are get rid of..." and line 27, which recites "enbryonic".

Appropriate correction is required.

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: The brief description of the figures in the specification Figure 2A and 2B. However, the drawings disclosure Figure 2 and Figure 2 continued and does not disclose A and B. Amending the drawing to designate A and B would be remedial. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required

corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

Claims 1-9, 15, 16, 4-42, 45, 49, and 70-75 are objected to because of the following informalities: These claims comprise non-elected subject matter. Applicant must amend the claims to solely encompass the elected subject matter of group II. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 40-42, and 49 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3-7 of copending Application No. 11/547,871. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of the instant claims are disclosed by the methods of the copending claims.

Copending claim 3 discloses an assay system that cultivates a biological material derived from tissue or tissue-like structures obtained by culturing an ES cell derived first cell type in the presence of at least one embryonic second cell type. Claim 1 of the instant claims is drawn to the method of making the above described biological material. Thus, it would be obvious to an artisan that the method step disclosed in claim 3 of the copending application is the same method as claim 1 of the instant application. Dependent claims 4-7 of the copending application are essentially identical to dependent claims 2-5 of the instant application. Claim 40 of the instant application further comprises analyzing physiological status of the tissue or tissue-like structure. Claim 41 and 42 of the instant application specify that the analyzing step encompasses measuring electrical activity with a microelectrode array. Copending claim 3 discloses measuring electrical activity with an electrode array. Thus, Copending claim 3 discloses the same scope of claims 40-42 of the instant application. Claim 49 of the instant application discloses the use of tissue system of claim 1 for analyzing the influence of factors and compounds. These limitations are disclosed as an intended used in the preamble of claim 3 of the copending application. Thus, it would be obvious to an

artisan of ordinary skill that the instant and copending claims of the two applications encompass the same invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, -6, 8-11, 15, 16, 26, 45, and 49 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3, 17, 21-24, 26-32, 47, 55, 57-62, 64-69, and 70 of copending Application No. 10/594,188. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims encompass overlapping, non-mutually exclusive scopes.

Copending claims 3 and 47 are drawn to method that cultures ES cells to form EB. Claim 1 of the instant application is drawn to a method that cultures a first embryonic-derived cell type with a second embryonic cell type and aligning or integrated the cell types to form a tissue-like structure. The breadth of claim 1 encompasses culturing a plurality of ES cells together because the claim does not specify that the first and second cell types are two different cell types. Claim 1 does not specify the characteristics of a "tissue-like structure". Thus, producing an EB, as claimed in copending claims 3 and 47, encompasses the limitations of aligning and integrating cells into a "tissue-like structure" of instant claims 1. Thus, Copending claims 3 and 47 encompass the same limitations as encompassed by instant claim 1. Copending claims 17 and 55 encompass the same limitations as instant claims 9 and 10 because both the

copending and instant claims specify that the method produce cardiomyocytes in the EB or tissue-like structure. Copending claims 21, 22, 24, 57, 58, and 60 encompass the same scope as instant claims 2 and 4 of the instant applications because both recites that the ES cell have a selectable marker and a reporter gene both operably linked to a tissue specific marker. Copending claims 23 and 59 have the same scope as instant claim 3 because specify the selectable marker as puromycin. Copending claims 26 and 62 and instant claim 6 specify the reporter gene is EGFP. Copending claims 27 and 61 and instant claim 5 encompass the same scope because all claims specify the tissue specific promoter is substantially the same for the selectable marker and the reporter gene. Copending claims 28 and 64 and instant claim 8 encompass the same scope because both claims specify that the marker and reporter gene are contained in the same cistron. Copending claims 29, 30, 65, 66, 69, and 70 of the copending application encompass the same scope as instant claims 11 and 26 because all the claims specify the promoter as a cardiac specific promoter, more specifically alpha-MHC or MLC2v. Copending claims 31, 32, 67, and 68 encompass an EB, cardiomyocytes, or tissue of cardiomyocytes. These limitations are a species of the co-culture of instant claim 15, the tissue of instant claim 16, and the tissue of instant claim 45. Instant claims 49 specifies intended use of the method of claim 1 and does not add any active steps to the method. Thus, copending claims 3 and 47 encompass the same scope as claim 49 for reasons discussed above. Overall, it would be obvious to an artisan that the claims of the instant and copending application encompass the same invention because they encompass overlapping, non-mutually exclusive scopes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 5, 7-16, 26, 40, 41, 45, 49, and 70-73 are rejected under 35 U.S.C. 102(b) as being anticipated by Muller (Muller et al. FASEB J 14:2540-2548; of record).

Given its broadest reasonable interpretation, claim 1 and dependents encompass a method of making an EB. Claim 1 species the coculture a first embryonic derived cell type with a second embryonic cell type. The breadth of these limitations encompasses the culture of two or more ES cell because the claims do not require that the first and second cell types be two different cell types. Claim 1 also specifies that the cells are allowed to align and integrate into a tissue or tissue like structure. Neither the claims nor the specification define "align", "integrate", or "tissue-like structure". Therefore, any formation, alignment, or interaction of the cells, such as EB formation, encompasses this limitation.

Muller discloses a method of culturing mouse ES cells to form EBs (p. 2542, col 1, lines1-12), thus disclosing the limitations of claim 1 and 13. These disclosures also

disclose the products of claims 15, 16, and 45. These disclosures also disclose the limitations of claim 49 because claim 49 recites an intended use for the method of claim 1 and does not impose further material limitations to the method, therefore does not impose addition patentable limitations. Muller discloses the before EB formation, a EGFP reporter gene operably linked to the cardiac specific promoter, CMVenh/MLC-2v was introduced and expressed by the ES cells (p. 2541, col 2, par 1 under "Transfection constructs", lines 19-22). These disclosures disclose the reporter gene limitations of claims 4, 6, 11, and 26. These disclosures also disclose the selectable marker limitations of claims 2, because a "selectable marker" can be anything that can be used to select, sort, choose, or discriminate a cell and EGFP can be used as such. Further, The claims do not require the "selectable marker" and the "reporter gene" be different entities. Therefore, the EGFP encompasses the limitations of both the selectable marker and reporter gene. As follows, the limitations of claim 5 is also met because the regulatory sequence of the marker and reporter gene are the same, and thus substantially the same as claimed. The limitations of claims 7 and 8 are met because the marker gene and the reporter gene are on the same nucleic acid molecule and cistron. Further, Muller discloses the use of ES cell transfected with the selectable marker gene, neomycin, operably linked to the cardiac alpha-MHC promoter to select cardiomyocytes and ES cell transfected with the a EGFP reporter gene operably linked the cardiac alpha-MHC promoter to select cardiomyocytes (p. 4541, col 1, lines 20-31). Thus Muller also discloses the use of a separate selectable marker, neomycin, and a reporter gene EGFP. These disclosures also encompass the limitations of claim 70.

Claim 70 required that the cell be genetically engineered to express a target gene. The breadth of "a target gene" can be any gene of interest. In the instant case, the neomycin and EGF encompass genes of interest and the cell were genetically engineered to express these genes of interest. Thus, Muller discloses claim 70. Muller discloses method of differentiating ES cell by EB formation and selecting cardiomyocytes from the EB (p. 4542, col 1, par 1. line 1 to par 2, line 8). These limitations disclose claims 9 and 10. Although Muller focuses on cardiomyocytes produced by EB formation, Muller acknowledges that this method results in spontaneous differentiation in vitro into a variety of cell lineages including endothelial cells and fibroblast cell (p. 4540, last line to line 4 of col 1 on p. 4541). Thus inherently the EB formation results in a coculture and alignment of multiple cell type (i.e.- 3 or more) in the EB culture. Thus, inherently the EB culture includes the additional cell types as claimed in claims 12-14. Claim 71 specifies the addition of a compound know to active or inhibit the differentiation process in the culture medium. The breadth of this recitation encompasses the EB cultured medium itself because the culture medium is known to promote or activate EB formation. Muller discloses that the EB or beating areas was subjected to patch-claim experiments in container to analyze their electrophysiological status (p. 4522, col 2, section 'Preparation of single cells and electrophysiology'). These disclosures encompass the limitations of claims 40 and 72. Claim 41 specifies electrical measurement on an array. The breadth of an array encompasses multiple simultaneous measurements on multiple samples. This is taught by the disclosure of electrophysiological analysis. Thus, the limitations of claim 41 are

disclosed. Claim 73 specifies taking three or more measurement in claim 1, optionally at three different positions within the container. The claims do not specify what is to be measured and the positions of measurement are optional. Thus any type of measurement will encompass the limitations of this claim. Muller discloses the measurement of alpha-actinin, skeletal myosin, and anti-tropin I expression by immunofluorescence labeling (p. 4542, col 2, par 3 and 4). Muller discloses measurement of cardiomyocytes by FACS analysis (p. 4542, col 2, last par). Muller discloses electrophysiological measurements, as discussed above. Thus, Muller discloses more than three measurements and discloses the limitations of claim 73.

Thus, Muller clearly anticipates the claims because Muller discloses all the patentable limitations of the claims.

Claims 1, 2, 3-5, 7-16, 26, 40, 41, 45, 49, and 70-74 rejected under 35 U.S.C. 102(b) as being anticipated by Franz (US Patent 5,928,943 patent date:7/27/1999).

The instant rejection encompasses the same claim interpretation as discussed in the Muller rejection.

Franz discloses a method of culturing and producing EB with ES cells that comprise an expression vector encoding the selectable marker, neomycin, and the reporter gene, beta galactosidase (beta-Gal) operably linked to the cardiac specific promoter, MLV-2v promoter (col 1, lines 21-23, lines 40-47, lines 52-53, and figure 1). Franz discloses that these ES cells are cultured using the hanging drop method to form

EB and that EB cultures are transferred into microtiter plates (col 3, lines 3-23). Franz discloses that expression of beta-Gal identifies cardiomyocytes cells, while expression of the selectable marker allows to a selection of cardiomyocytes differentiating cells over non-cardiomyocyte differentiating cells at an early stage in differentiation (col 3, lines 21-23 and lines 26-35). Franz discloses that the EB and cells are analyzed for electrophysiological function (col 3, lines 36-40).

Thus Franz clear anticipates the instant claims because Franz discloses all the patentable limitations of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 6, 42, and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Franz (cited above), in further view of Wantanabe (Wantanabe et al. Biochem Biophys Res Com 213(1):130-137, 1995), Muller (cited above) and Feld (Feld et al. Circulation 105:522-529, January 2002).

The instant rejection encompasses the same claim interpretation as discussed in the Muller 102(b) rejection.

Franz teaches a method of culturing and producing EB with ES cells that comprise an expression vector encoding the selectable marker, neomycin, and the

reporter gene, beta galactosidase (beta-Gal) operably linked to the cardiac specific promoter, MLV-2v promoter (col 1, lines 21-23, lines 40-47, lines 52-53, and figure 1). Franz teaches that these ES cells are cultured using the hanging drop method to form EB and that EB cultures are transferred into microtiter plates (col 3, lines 3-23). Franz teaches that expression of beta-Gal identifies cardiomyocytes cells, while expression of the selectable marker allows to a selection of cardiomyocytes differentiating cells over non-cardiomyocyte differentiating cells at an early stage in differentiation (col 3, lines 21-23 and lines 26-35). Franz teaches that the EB and cells are analyzed for electrophysiological function (col 3, lines 36-40).

Franz does not teach the selectable marker is a puromycin as claimed in claim 3. However, Watanabe teaches methods for selecting transfected ES cell containing puromycin genes. Thus it would have been obvious to an artisan of ordinary skill to substitute the neomycin gene of Franz with the functional equivalent, puromycin, taught by Watanabe, in order to achieve the predictable result of selecting transfected functionally drug resistance.

Franz does not teach the EGFP reporter gene as claimed in claim 6. However, Muller teaches the use of ES cell comprising a EGFP gene operably linked to the cardiac specific promoter, MLV-2v promoter, to identify ES cell that differentiate into cardiomyocytes (p. 4541, col 1, lines 20-31). Further Muller demonstrates the superiority of EGFP as a reporter gene because it allows for identification and sorting of live cardiomyocytes by FACS (p. 4542, col 2, last par). Thus, it would have been obvious to an artisan of ordinary skill to simply substitute the beta-Gal reporter gene of

Franz with the function equivalent, EGFP gene taught by Muller, in order to achieve the predictable result of expressing cardiomyocyte specific reporter. Further, an artisan would be motivated to do such a substitution because EGFP allows for monitoring and sorting live cardiomyocytes, whereas beta-Gal does not.

Franz does not teach recording the extracellular potential with a MEA, as claimed in claim 42. However, Feld discloses a method of measuring extracellular potential in multicellular cardiac grafts using MEA (p. 523, col 1, section 'Multielectrode Mapping Technique', par 1, line 1 to col 2, lines 2). Thus, it would have been obvious to an artisan of ordinary skill that an artisan to choose MEA, as taught by Feld, from a finite number of predictable methods of measuring extracellular potential with a reasonable expectation of successfully measuring extracellular potential in the tissue cultures of the instant claims.

Franz does not specifically teach the use of 24-, 96-, 384-, or 1586- well plate, as claimed in claim 75. However, at the time of the invention it would have been obvious to an artisan of ordinary skill to choose from a finite number of a micro titer plate designs comprising the number of well needed to accommodate their EB culture of Franz depending upon the intended use of the culture with a reasonable expectation of success.

The combination of prior art cited above in all rejections under 35 U.S.C. 103 satisfies the factual inquiries as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Once this has been accomplished the holdings in KSR can be applied (*KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. ___, 82 USPQ2d 1385

(2007): "Exemplary rationales that may support a conclusion of obviousness include: (A) Combining prior art elements according to known methods to yield predictable results; (B) Simple substitution of one known element for another to obtain predictable results; (C) Use of known technique to improve similar devices (methods, or products) in the same way; (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results; (E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention."

In the present situation, rationales A-E and G are applicable. The claimed method was known in the art at the time of filing as indicated by Franz, Wantanabe, Muller, and Feld. Thus, the teachings of the cited prior art in the obviousness rejection above provide the requisite teachings and motivations with a clear, reasonable expectation. The cited prior art meets the criteria set forth in both Graham and KSR.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16, 26, 40-42, 45, 49, and 70-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and its depend claims recite, "a tissue-like structure". This recitation is indefinite because it is not apparent how closely and in what manner the structure is to resemble a tissue. Amending the claims to include specific structural properties that make a "tissue-like structure" may be remedial.

Claim 40 and its dependent claims 41 and 42 recite the limitation "the...cell aggregates". There is insufficient antecedent basis for this limitation in the claim.

Claim 73 recites the limitation "the container". There is insufficient antecedent basis for this limitation in the claim.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCIA S. NOBLE whose telephone number is (571)272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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